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PATENT APPLICATION

ATTORNEY DOCKET NO. 2001-0878.ORI

UNITED STATES PATENT AND TRADEMARK OFFICE

Date	:	January 20, 2006
Re App	:	Alexander James Wigmore
Serial No.	:	09/831,681
Filed	:	May 10, 2001
Title	:	TREATMENT FOR ALLERGIC CONDITIONS
Art Unit	:	1615
Examining Attorney	:	Susan T. Tran

RESPONSE

Attn: Board of Appeals and Interferences

Appellant's Brief (37 C.F.R. §41.37)

Attached herewith is a corrected Appeal Brief in response to the Notification of Non-Compliant Appeal Brief mailed on December 21, 2005. The Brief has been corrected herein to comply with 37 CFR §41.37(c).

Respectfully submitted,

HAUGEN LAW FIRM PLLP

Date: January 20, 2006

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PATENT APPLICATION

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APPEAL BRIEF

Attn: Board of Appeals and Interferences

Appellant's Brief (37 C.F.R. §41.37)

This Appeal Brief is submitted in furtherance of the Notice of Appeal filed on December 22, 2004 and received by the USPTO on December 28, 2004 in the above-identified application.

This Brief contains the following items under the headings and in the order set forth below (37 C.F.R. §41.37(c)(1)):

i. Real Party in Interest
ii. Related Appeals and Interferences
iii. Status of Claims
iv. Status of Amendments
v. Summary of Claimed Subject Matter
vi. Grounds of Rejection to be Reviewed on Appeal
vii. Argument
viii. Appendix of Claims
ix. Appendix of Evidence
x. Appendix of Related Proceedings

1. **Real Party in Interest (37 C.F.R. §41.37(c)(1)(i)):**

The real party in interest with respect to the above patent application is Hewlett Healthcare Limited of Melbourne, Derby, United Kingdom.

2. **Related Appeals and Interferences (37 C.F.R. §41.37(c)(1)(ii)):**

There are no other appeals or interferences known that are related to the above patent application.

3. **Status of Claims (37 C.F.R. §41.37(c)(1)(iii)):**

The claims in the application are 1-36. Of these claims:

Claims 10-15 and 17-29 are withdrawn from further consideration;

Claims 6, 31, and 32 are cancelled

Claims 1-5, 7-9, 16, 30, and 33-36 are pending;

Claims 1-5, 7-9, 16, 30, and 33-36 stand rejected.

The claims on appeal are 1-5, 7-9, 16, 30, and 33-36.

4. **Status of Amendments (37 C.F.R. §41.37(c)(1)(iv)):**

Claims 1-5, 7-9, 16, 30, and 33-36 were finally rejected in an Office Action dated August 23, 2004.

5. **Summary of the Claimed Subject Matter (37 C.F.R. §41.37(c)(1)(v)):**

The pending claims recite oral drug compositions that are useful in treating food allergies in human patients by delivering the drug at the small intestine and preferably

at the upper jejunum portion of the small intestine. The claimed compositions include a chromone drug and a disintegrant, with the disintegrant material being present at a critical concentration in order to effect rapid dissolution of the compositions and release of the chromone drug upon exposure to intestinal fluid.

Claim 1

Claimed Subject Matter	Specification Location
An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to simulated gastric fluid, and (2) at least 15% of the chromone dissolves within 10 minutes of subsequent exposure of the composition to simulated intestinal fluid	Page 4 lines 7-15; Page 7 lines 11-14
said composition further comprising disintegrant at a raitio of at least 1.2:1(w:w) of disintegrant to chromone	Page 13 lines 22-25
wherein said disintegrant is selected from the group consisting of microcrystalline cellulose, croscarmellose sodium, crosprovidone, sodium starch glycolate, and combinations thereof.	Page 15 line 22- Page 16 line 14

Claim 8

Claimed Subject Matter	Specification Location
An oral drug delivery composition comprising a chromone.	Page 4 lines 7-8
wherein the composition further comprises disintegrant at a ratio of at least 1.5:1 (w:w) of disintegrant to chromone.	Page 13 lines 22-25

Claim 34

Claimed Subject Matter	Specification Location
An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to simulated gastric fluid, and (2) at least about 80% of the chromone dissolves within about 5 minutes of subsequent exposure of the composition to simulated intestinal fluid	Page 4 lines 7-15
said composition further comprising microcrystalline cellulose	Page 16, line 8
at a ratio of at least 1.4:1 (w:w) of microcrystalline cellulose to chromone.	Page 13 lines 22-25

Claim 35

Claimed Subject Matter	Specification Location
An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to simulated gastric fluid, and (2) at least about 27% of the chromone dissolves within about 10 minutes of subsequent exposure of the composition to simulated intestinal fluid	Page 4 lines 7-15
said composition further comprising disintegrant at a ratio of at least 1.2:1 (w:w) of disintegrant to chromone	Page 13 lines 22-25
wherein said disintegrant is selected from the group consisting of croscarmellose sodium, crosprovidone, sodium starch glycolate, and a blend of croscarmellose sodium and microcrystalline cellulose at a ratio of about 1:9 (w:w) of croscarmellose sodium to microcrystalline cellulose.	Page 15 line 22 - Page 16 line 23

Claim 36

Claimed Subject Matter	Specification Location
An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to simulated gastric fluid, and (2) at least about 21% of the chromone dissolves within about 5 minutes of subsequent exposure of the composition to simulated intestinal fluid	Page 4 lines 7-15
Said composition further comprising disintegrant at a ratio of at least 1.4:1 (w:w) of disintegrant to chromone	Page 13 lines 22-25
wherein said disintegrant is selected from the group consisting of super disintegrants in the form of a cross-linked cellulose, a cross-linked polymer, a cross-linked starch, and microcrystalline cellulose.	Page 15 line 22 - Page 16 line 23

6. **Grounds of Rejection to be Reviewed on Appeal (37 C.F.R. §41.37(c)(1)(vi)):**

A. Whether Claims 1-5, 7-9, 16, 30, and 33-36 are unpatentable under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

B. Whether Claims 1-5, 7-9, 16, 30, and 33-36 are unpatentable under 35 U.S.C. § 103(a) over Watts et al. (U.S. 6,200,602).

7. **Argument (37 C.F.R. §41.37(c)(1)(vii)):**

A. Rejection under 35 U.S.C. §112, First Paragraph.

Applicant respectfully submits that all appealed claims are supported by the specification as originally filed, and further clarified in the Declaration under 37 C.F.R. §1.132 submitted on May 29, 2003 ("Exhibit A" in Appendix of Evidence). However, certain groups of the claims on appeal find distinct sets of supporting documentation under 35 U.S.C. §112, and are therefore separately patentable. Therefore, should any one of the claim groups set forth below be considered by the Board to not be properly supported under §112, its rejection should

not obscure a de novo review of the remaining claim groups. The Examiner has finally rejected Claims 1-5, 7-9, 16, 30, and 33-36 under 35 U.S.C. §112, first paragraph, and has asserted that the specification does not provide support for the pending claims, and particularly for the recited chromone dissolution rates in simulated intestinal fluid.

1. Claims 1-5, 7, 9, 16, 30, and 33.

Claim 1 recites a composition including a chromone wherein at least 15% of the chromone dissolves within 10 minutes of exposure of the composition to simulated intestinal fluid. The application at page 4, lines 11-15 explicitly describe the claimed chromone dissolution rate in simulated intestinal fluid in stating "from 15% ... of the chromone dissolves within 10 ... minutes of subsequent exposure of the composition to simulated intestinal fluid". The embodiment recited in Claim 1 includes a disintegrant to chromone ratio of at least 1.2:1, which corresponds to a chromone dissolution rate of at least 15% within 10 minutes of exposure of the composition to simulated intestinal fluid.

2. Claims 34-36.

Claim 34 is also explicitly described in such passage of the application as originally filed by stating that "from ... 80% ... of the chromone dissolves within ... 5

... minutes of subsequent exposures of the composition to simulated intestinal fluid". The dissolution recitation in Claim 34 merely represents one embodiment of the many embodiments described at page 4, lines 7-15 of the application, with the dissolution rates being related to the concentration ratio of disintegrant to chromone in the claimed composition. For example, the concentration ratio of disintegrant to chromone in Claim 34 is at least 1.4:1, specifically of microcrystalline cellulose to chromone. At such a concentration ratio, the chromone dissolution rate in simulated intestinal fluid is at least about 80% within about 5 minutes of exposure of the composition to simulated intestinal fluid.

The Examiner states in the Official Action dated August 23, 2004 that the specification does not provide support for the limitation "at least about 80% of the chromone dissolves within about 5 minutes", since the specification discloses a lower limit as low as 15%. It is well established law that an applicant need not claim all that he is entitled to claim, and that there is no requirement that the Applicant demonstrate the criticality of a lower limit in a particular claim to meet the description requirement (see In re Eichmeyer, 602 F.2d 974, 981 (CCPA 1979)). Moreover, it has been held that the

written description of a broad range of characteristics adequately supports claims to a narrower range thereof (In re Wertheim, 541 F.2d 257, 265 (CCPA 1976)). The presently pending claims, and specifically Claims 34-36, represent relatively narrow claims in view of the broad range described at page 4 of the specification. Namely, the chromone dissolution rate of about 80% within about 5 minutes in Claim 34 is within the described range of between 15 and 100% dissolution within between 1 and 30 minutes, as described at page 4, lines 11-15 of the specification.

The Court in In re Wertheim, 541 F.2d 257, 265 (CCPA 1976) dealt with a parent application describing a material concentration of 25 to 60% with specific examples of 36% and 50%. The claims in question in In re Wertheim specify a concentration of "between 35% and 60%". The Court held that the Patent and Trademark Office failed to establish a prima facie case of noncompliance with the written description requirement under §112 (In re Wertheim, 541 F.2d at 265). Contrary, therefore, to the Examiner's assertion in the Official Action of August 23, 2004, the In re Wertheim ruling demonstrates that a claim range may be duly supported under 35 U.S.C. §112 even though it may not encompass the lower limit described in the specification.

This doctrine is further set forth in Kolmes v. World Fibers Corp., 107 F.3d 1534 (Fed. Cir. 1997), wherein the Court found that a claim limitation of "8-12 turns per inch" is well supported by the specification which discloses a rate of "4-12 turns per inch" Id. at 1539. It clearly follows that the presently pending claims, which recite dissolution rates within the ranges described in the specification as originally filed, are adequately supported thereby under 35 U.S.C. §112, first paragraph. As such, the claim recitation of "at least about 27%" and "at least about 21%" of chromone dissolution in Claims 35 and 36, respectfully, find adequate support in the specification as originally filed at page 4, lines 7-15.

In addition to the above, Exhibit A provides supplemental data for the dissolution of chromone upon exposure of the composition to simulated intestinal fluid. Specifically, page 5 of Exhibit A defines five distinct blends having different disintegrant to chromone ratios, wherein Batch 2 represents a 1.2:1 disintegrant to chromone ratio, and Batch 3 represents a 1.4:1 disintegrant to chromone ratio. As shown on pages 7 and 8 of Exhibit A, through either a paddle or basket method, the claim limitations contained in the pending claims are reinforced by experimental results. For example, at a disintegrant to

chromone ratio of 1.2:1 (Batch 2), 87.1% of the chromone dissolved within 10 minutes of exposure in a paddle method, and 93.4% of the chromone dissolved within 10 minutes in the basket method, wherein the disintegrant utilized was microcrystalline cellulose. Such results demonstrate that, in a composition having a disintegrant to chromone concentration ratio of 1.2:1, at least 15% of the chromone dissolves within 10 minutes of exposure of the composition to simulated intestinal fluid, as is recited in pending Claim 1. Moreover, "Batch 3", which represents a disintegrant to chromone ratio of 1.4:1, is demonstrated on pages 7 and 8 of Exhibit A as having 99.7 or 99.1% chromone dissolution within 5 minutes of exposure to simulated intestinal fluid, depending upon the method utilized. Such a chromone dissolution rate is clearly within the recited range of pending Claim 34.

In addition, the chromone dissolution rate recited in Claims 35 and 36 are specifically demonstrated by the experimental results attached to Applicant's response dated April 30, 2004 ("Exhibit B" in Appendix of Evidence). Specifically, the composition recited in Claim 35 is demonstrated in the results by "Blend 2", such that across each of formulations 1-4 in the attached experimental results, at least about 27% of the chromone dissolves

within about 10 minutes of exposure of the composition to simulated intestinal fluid. Likewise, the composition recited in Claim 36 is analogous to that described with reference to "Blend 3" in Exhibit B. In each of the experiments conducted, Blend 3 had a chromone dissolution rate of at least about 21% within 5 minutes of exposure of the composition to simulated intestinal fluid. Accordingly, each of the claimed dissolution rates find specific and sufficient support in the specification as originally filed, and are clearly demonstrated in the experimental results provided in Exhibits A and B.

3. Claims 1-5, 7-9, 16, 30, and 33-36.

The specification as originally filed describes at page 13, lines 22-25 the preferred disintegrant to chromone ratios that provide the rapid dissolution of chromone in simulated intestinal fluid. This passage again defines a range of concentration ratios within which the pending claims define respective narrower ranges. Such a claim methodology fully complies with 35 U.S.C. §112, first paragraph, and as described above with reference to In re Wertheim, 541 F.2d 257 (CCPA 1976) and Kolmes v. World Fibers Corp., 107 F.3d 1534 (Fed. Cir. 1997).

Moreover, Exhibits A and B specifically demonstrate obtaining the claimed chromone dissolution rate through the

use of various disintegrant to chromone ratios, so long as such ratios are within the critical range of disintegrant to chromone ratios defined in the specification at page 13. As such, the claimed disintegrant to chromone concentration ratios are fully supported under 35 U.S.C. §112, first paragraph by the specification as originally filed.

4. Claims 1-5, 7, 9, 16, 30, and 33-36.

The Examiner asserts in the Official Action dated August 23, 2004 that the specification does not provide support for the disintegrants cited in Claims 1 and 34-36. However, Applicant submits that such disintegrant materials are specifically identified at page 15, line 22 through page 16, line 21.

In addition, the experimental results included in Exhibits A and B demonstrate the utilization of the claimed disintegrant materials. In particular, the disintegrant materials recited in Claims 35 and 36 are discussed with reference to the experimental results of Exhibit B. Namely, "Formulation 1" includes croscarmellose sodium, "Formulation 2" includes crosprovidone, "Formulation 3" includes sodium starch glycolate, and "Formulation 4" includes a combination of croscarmellose sodium and microcrystalline cellulose at a weight concentration ratio

of 1:9 respectively. Such disintegrant materials are specifically recited in Claims 35 and 36.

As demonstrated above, the currently pending claims clearly find support in the specification as originally filed, and therefore comply with the requirements of 35 U.S.C. §112, first paragraph.

B. Rejection Under 35 U.S.C. §103(a) over U.S. Patent No. 6,200,602.

The Watts et al. '602 patent is generally directed to a drug composition for delivery in the colon of the user. In particular, Watts et al. '602 disclose a composition that prevents release of the drug until the formulation reaches the colon (column 6, lines 21-24).

1. The Watts et al. '602 fails to teach or suggest the claimed disintegrant to chromone ratios recited in each of Claims 1-5, 7-9, 16, 30, and 33-36.

The primary essence of the present invention is in providing an oral drug delivery composition that is formulated to pass through the patient's stomach substantially intact, and to subsequently rapidly disperse and dissolve upon exposure to intestinal fluid (see page 7, line 11 - page 8, line 2 of the application). As described in the above-cited passage, such rapid dissolution of the composition enables a relatively high concentration of the drug to be delivered to the upper portion of the small

intestine where it can best treat allergic conditions relating to ingested substances.

A conventional enteric coating may optionally be utilized on the composition of the present invention to prevent premature dissolution while passing through the gastric fluid of the stomach. Once inside the intestinal fluid environment, the enteric coating dissolves, exposing the underlying composition of the present invention. At this point, the claimed disintegrant to chromone ratios enable the chromone to rapidly dissolve in the intestinal fluid. Compositions of the prior art, by contrast, fail to rapidly disperse in the small intestine, possibly due to a gel that forms about the drug when exposed to intestinal fluid (page 3, lines 12-27 of the application; see also page 1 lines 21-23 of GB2,086,227 cited in Applicant's Information Disclosure Statement filed on July 9, 2001 ("Exhibit C" in Appendix of Evidence)).

The gelling effect observed of drug delivery compositions of the prior art has been surprisingly overcome through the use of specific ratios of disintegrant material to the chromone that is present in the composition. In doing so, the chromone is allowed to rapidly disperse and dissolve in the intestinal fluid (see page 17, lines 10-23 of the application). Nowhere,

however, do Watts et al. '602 teach or suggest the presently claimed ratios of disintegrant material to chromone.

(i) The disintegrant material to chromone ratios recited in Claims 1-5, 7-9, 16, 30, and 33-36 are critical to the operation of the invention.

The Examiner argues that concentration differences between the present claims and the prior art do not support patentability unless there is evidence indicating that such concentration differences are critical. Here, the relative concentrations of the disintegrant to chromone in the compositions of the present invention are indeed critical to the rapid dissolution characteristic that is central to the utility of the claimed compositions. Such criticality of the disintegrant to chromone ratios is described at page 17, lines 10-23 of the application, as well as in paragraph 5 of Exhibit A. Specifically, Mr. Wigmore states in Exhibit A that "the amount of disintegrant (for example microcrystalline cellulose) in the sodium cromoglycate tablet formulation was critical to the dissolution performance of the tablet." In reporting the findings represented in the present application, Mr. Wigmore stated on page 4 of Exhibit A that it is critical to include a disintegrant to chromone ratio of at least 1.2 to 1 and

more beneficially at least 1.4 or 1.5 to 1. "This is far in excess of the quantity of disintegrants conventionally used in tablets" (Exhibit A). The Applicant has clearly attested to the fact that the claimed disintegrant to chromone ratios are indeed critical to the compositions of the present invention.

2. The Watts et al. '602 patent fails to teach or suggest the chromone dissolution rates recited in Claims 1-5, 7, 9, 16, 30, and 33-36.

The Examiner argues on page 4 of the Official Action dated August 23, 2004 that the disclosure in Watts et al. '602 of an enteric coating material supports a prima facie case of obviousness, specifically in that the enteric coated tablet of Watts et al. '602 would have similar dissolution rates recited in the pending claims. Applicant submits, however, that the Examiner confuses the dissolution of the enteric coating with the presently claimed dissolution rates of the chromone. Specifically, an enteric coating incorporated over the compositions of the present invention would indeed likely have a similar dissolve rate in intestinal fluid as the enteric coating described in Watts et al. '602 (though Watts et al. '602 at column 6 lines 21-60 teaches the use of an enteric coating thickness that will not completely dissolve until the

composition reaches the colon). The dissolution rate of an enteric coating, however, is independent of the dissolve rate of the drug itself, which drug, in the case of Watts et al. '602, is disposed underneath the enteric coating. Therefore, it is not the dissolve rate of an enteric coating that is now being claimed in the present application, but rather the dissolution rate of the chromone drug itself into simulated intestinal fluid. Applicant respectfully submits that no teaching is found in Watts et al. '602 of the chromone dissolution rates now claimed. As stated above, the problem associated with compositions of the prior art that is now overcome by the present invention is the slow dissolution of the drug once it is exposed to intestinal fluid.

It is well established that the Examiner must establish a prima facie case of obviousness in order to support a claim rejection under 35 U.S.C. §103. "In rejecting claims under 35 U.S.C. §103 the Examiner bares the initial burden of presenting a prima facie case of obviousness" In re Rijckaert, 9 F.3d 1531, 1532 (Fed. Cir. 1993). The Court in In re Rijckaert further states that "[a] prima-facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of

ordinary skill in the art" In re Rijckaert, 9 F.3d at 1532. Here, since no suggestion is found in Watts et al. '602 of either the presently claimed critical disintegrant to chromone ratios or the chromone dissolution rates, the Examiner has failed to establish a prima facie case of obviousness. Only if the Examiner's initial burden of establishing a prima facie case of obviousness is met does the burden of coming forward with evidence or argument shift to the applicant (In re Rijckaert, 9 F.3d at 1532). As such, Applicant bears no burden, as the Examiner argues, to demonstrate the properties of Watts et al. '602.

C. Conclusion

For the foregoing reasons, Claims 1-5, 7-9, 16, 30, and 33-36 are unobvious and patentable over the cited prior art. Applicant therefore submits that all pending claims are allowable on the merits and respectfully requests allowance thereof.

Respectfully submitted,

HAUGEN LAW FIRM PLLP

Date: January 20, 2006

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8. **Appendix of Claims on Appeal (37 C.F.R. §41.37(c)(1)(viii):**

1. An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to simulated gastric fluid and (2) at least 15% of the chromone dissolves within 10 minutes of subsequent exposure of the composition to simulated intestinal fluid, said composition further comprising disintegrant at a ratio of at least 1.2:1 (w:w) of disintegrant to chromone wherein said disintegrant is selected from the group consisting of microcrystalline cellulose, croscarmellose sodium, crosprovidone, sodium starch glycolate, and combinations thereof.

2. A composition according to claim 1 wherein the composition is formulated as a tablet.

3. A composition according to claim 2 wherein the tablet has an enteric coating.

4. A composition according to claim 2 or 3 wherein the composition is still in the form of a tablet at the end of the exposure of the composition to gastric fluid.

5. The composition according to any one of claims 2 to 4 wherein the tablet comprises between about 50mg and 200mg of chromone.

7. A composition according to claim 1 wherein the composition comprises substantially spherical pellets of up to 5 mm diameter comprising the chromone, each pellet having an enteric coating.

8. An oral drug delivery composition comprising a chromone wherein the composition further comprises disintegrant at a ratio of at least 1.5:1 (w:w) of disintegrant to chromone.

9. A composition according to claim 1 or claim 8 wherein the ratio of disintegrant to chromone is between about 1.5:1 and 2.5:1

16. A composition according to any one of claims 1, 8, or 9 wherein the disintegrant is microcrystalline cellulose.

30. A composition according to any one of the preceding claims further comprising an amphoteric surfactant or a surfactant having a hydrophile-lipophile balance (HLB) value of less than about 10.

33. A composition according to any one of the preceding claims wherein the chromone is sodium cromoglycate.

34. An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to

simulated gastric fluid, and (2) at least about 80% of the chromone dissolves within about 5 minutes of subsequent exposure of the composition to simulated intestinal fluid, said composition further comprising microcrystalline cellulose at a ratio of at least 1.4:1 (w:w) of microcrystalline cellulose to chromone.

35. An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to simulated gastric fluid, and (2) at least about 27% of the chromone dissolves within about 10 minutes of subsequent exposure of the composition to simulated intestinal fluid, said composition further comprising disintegrant at a ratio of at least 1.2:1 (w:w) of disintegrant to chromone, wherein said disintegrant is selected from the group consisting of croscarmellose sodium, crosprovidone, sodium starch glycolate, and a blend of croscarmellose sodium and microcrystalline cellulose at a ratio of about 1:9 (w:w) of croscarmellose sodium to microcrystalline cellulose.

36. An oral drug delivery composition comprising a chromone wherein (1) not more than 10% of the chromone dissolves after two hours exposure of the composition to simulated gastric fluid, and (2) at least about 21% of the chromone dissolves within about 5 minutes of subsequent

exposure of the composition to simulated intestinal fluid, said composition further comprising disintegrant at a ratio of at least 1.4:1 (w:w) of disintegrant to chromone, wherein said disintegrant is selected from the group consisting of super disintegrants in the form of a cross-linked cellulose, a cross-linked polymer, a cross-linked starch, and microcrystalline cellulose.

9. **Appendix of Evidence (37 CFR §41.37(c)(1)(ix)**:

Exhibit A

Declaration of Alexander James Wigmore under 37 CFR §1.132 submitted on May 29, 2003, and indicated as being entered by the Examiner in an Office Action dated October 31, 2003.

Exhibit B

Experimental results submitted on April 30, 2004, and indicated as being entered by the Examiner in a Final Office Action dated August 23, 2004.

Exhibit C

British Patent No. 2,086,227 submitted on July 9, 2001, and indicated as being entered by the Examiner in an Office Action dated September 9, 2002.

EXHIBIT A

Declaration of Alexander James Wigmore
under 37 CFR §1.132 Submitted on May 29, 2003

PATENT APPLICATION

Docket No. 2001-0878.ORI

UNITED STATES PATENT AND TRADEMARK OFFICE

Re App : Alexander James Wigmore Date: Dec. 9, 2002

S.N. : 09/831,681 Group Art: 1615

Filed : May 10, 2001 Examiner: S.T. Tran

For : CHROMONE ENTERIC RELEASE FORMULATION

Commissioner for Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Declaration Of Alexander James Wigmore

Sir:

I, Alexander James Wigmore, hereby declare as follows:

1. That I am a citizen of the United Kingdom, and an employee of Hewlett Healthcare Limited, West View, The Common, Melbourne, Derbys, DE73 1DH, UK, and am the inventor of the claimed subject matter in the above-identified application for United States Letters Patent;

2. That I have been engaged in the development, assessment, and introduction of pharmaceutical compositions for the treatment of diseases of the respiratory system, eyes, gastrointestinal tract (GIT), and skin for a period of about twenty-six (26) years. Specifically, I have been

engaged in the development of many different formulations of sodium cromoglycate (scg) and related compounds for the treatment of various diseases;

3. That in the course of these activities, I have personally come familiar with the problems encountered with the bioavailability of pharmaceutically active drugs in the GIT;

4. That I have become familiar with the subject matter of the references cited by the Examiner in the course of prosecution, including U.S. Patent No. 6,200,602, and have related the substance of the presently claimed subject matter to the disclosures of the above reference;

5. That the subject matter of the cited reference does not provide the unexpected benefit of the presently claimed compositions, with the reasons being as follows:

The results from using scg in the GIT in the treatment of inflammatory bowel disease and food allergy have been variable, with some authorities reporting good effects and others variable or poor results. Clinical studies have failed to confirm that the oral formulation of scg is adequately effective. Since 1996 my company, Hewlett Healthcare Ltd., has been investigating possible reasons for this lack of efficacy and has discovered that the

problem is a lack of bioavailability of the drug in the GIT.

The lack of bioavailability is caused by a strange physical phenomenon demonstrated by scg in aqueous solutions. At pH 5 to 7 and at concentrations of greater than 7% scg produces a strong and tenacious gel. We discovered that the effect of this gel on a gastrointestinal formulation such as an scg tablet is such that an scg gel coat develops around the tablet preventing further ingress of water and so preventing the tablet from disintegrating and thus preventing the contents from becoming bioavailable. Indeed, the gel is so strong that in our initial tests, when a conventionally manufactured scg tablet was placed in water, the gel prevented the tablet from disintegrating for days and sometimes weeks.

We therefore investigated ways in which the effect of this gelling could be overcome and I unexpectedly discovered that it was necessary to include in the tablet a very high proportion of disintegrant to overcome the cohesive effect of the scg gel and allow the tablet to disintegrate and make the contents bioavailable. I found that the amount of disintegrant (for example microcrystalline cellulose) in the sodium cromoglycate tablet formulation was critical to the dissolution

performance of the tablet. I investigated the effect of varying the proportion of disintegrant to scg in the tablet and found a critical disintegrant to scg ratio of at least 1.2 to 1, more beneficially at least 1.4 or 1.5 to 1, as discussed in the patent application. This is far in excess of the quantity of disintegrant conventionally used in tablets. Normally 15% of the total tablet weight might be disintegrant with an upper normal limit of 20%. The ratio necessary to overcome the gelling forces has in contrast been found to be, for example, at least 47% of the total weight of the tablet (1.4:1 disintegrant to scg ratio). At a 1.76:1 disintegrant to scg ratio disintegrant represents 63% of the total tablet weight.

We would also point out that the mechanism of the disintegration of the tablet should not be confused with the properties of enteric coating. Enteric coating protects a tablet in the acid environment of the stomach enabling it to pass through the stomach intact. Once in the alkaline environment of the small intestine the enteric coat dissolves allowing the tablets to disintegrate but, due to the effect of the scg gel in scg tablet will not dissolve very easily and the critical part of the jejunum will be passed before the tablet is able to release the scg and the substance become bioavailable. This critical ratio

of scg granule to disintegrant ensures the tablet will disintegrate ***quickly*** after the enteric coat has dissolved, which it otherwise would not do. U.S. Patent No. 6,200,602 does not disclose such a critical ratio of disintegrant to scg, nor does it suggest the unexpected drug bioavailability increase effected through the compositions of the present invention.

The blend ratio between the scg and MCC is critical to the performance of the tablet. A tablet with insufficient disintegrant would fail to overcome the gelling effect of scg and the tablet would dissolve slowly.

The dried granules were used to make the following blends. Table 1 lists the blend formulations.

Table 1: Actual Blend Formulations

Blend No.	SCG Granules	MCC	Magnesium Stearate	(Granule-H_2O) : MCC Ratio
1	51.63	47.89	0.58	1:1
2	47.20	52.33	0.48	1:1.2
3	43.39	56.12	0.49	1:1.4
4	40.61	59.39	0.00	1:1.58
5	40.41	59.10	0.49	1:1.58

For the dissolution study, a tablet was placed in the dissolution vessel (paddle) or in the basket. The speed controller was switched on, set to the desired speed and the paddle or basket slowly lowered into the dissolution medium. Dissolution apparatus parameters are listed in Table 2.

A 5ml sample of dissolution medium was removed from the vessel at 5-minute intervals and placed into a labeled sample vial.

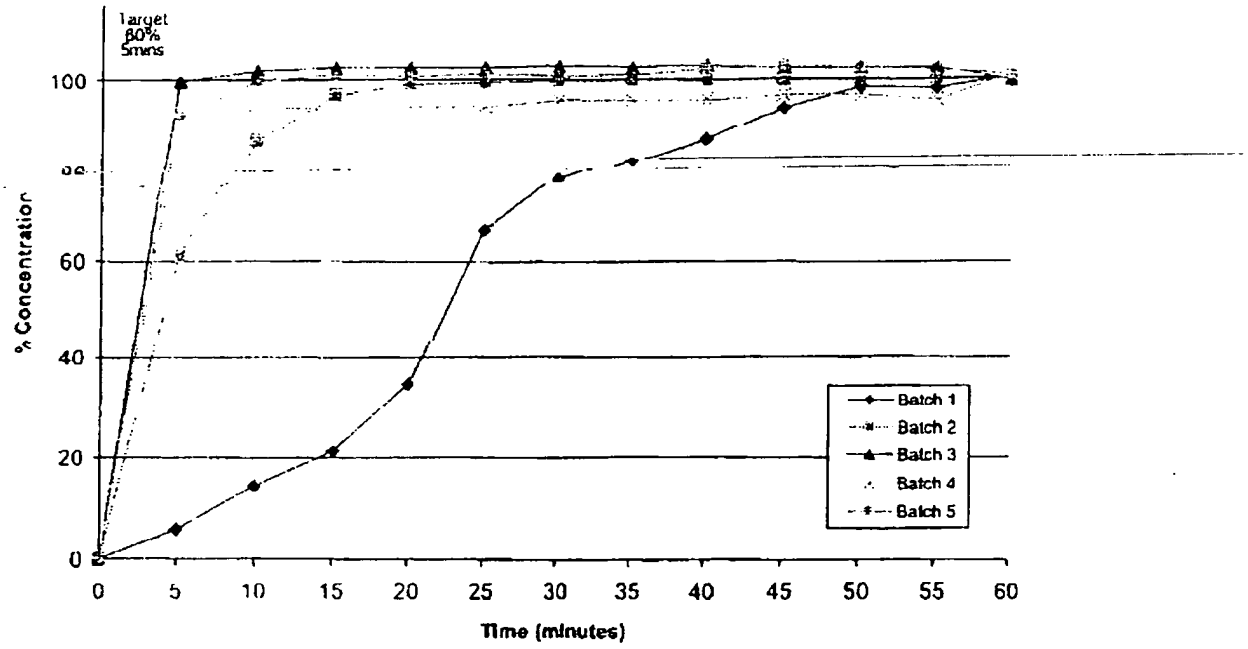
Table 2: Dissolution Apparatus Operating Parameters

Parameter	Details
Apparatus:	Paddle & Basket
Media:	Phosphate Buffer pH 6.8
Temperature:	37°C±0.5°C
Speed:	100rpm±
Test Duration:	60 mins

The HPLC assay method used to analyse the dissolution samples was listed.

The dissolution data for tablets from each blend were normalized to account for the different amounts of scg in each blend. The dissolution profiles of the tablets were then prepared by plotting SCG concentration versus time. Finally, the mean dissolution values were plotted against each other to allow the comparison of each blend.

Study to investigate the effect of various ratios of MCC to SCG and other excipients and their effect on the disintegration of SCG tablets – paddle method



Time	% Sample Concentration				
	Batch 1 —●—	Batch 2 —■—	Batch 3 —▲—	Batch 4 —×—	Batch 5 —✱—
0	0	0	0	0	0
5	5.9	60.7	99.7	87.4	92.4
10	14.1	87.1	101.8	94.5	99.7
15	21.3	96.8	102.4	93.8	100.8
20	34.8	99.0	102.5	94.3	100.7
25	66.3	99.3	102.5	94.5	101.3
30	77.4	99.5	102.7	95.6	100.5
35	82.5	99.7	102.6	95.8	100.7
40	87.3	99.5	102.7	95.8	102.3
45	94.2	99.6	102.3	96.6	102.4
50	98.2	99.5	102.2	96.8	102.1
55	98.1	99.6	102.0	95.7	101.9
60	100.1	100.0	99.6	100.5	100.5
Ratio (disintegrant to active)	Ratio 1.07:1	Ratio 1.36:1	Ratio 1.57:1	Ratio 1.76:1 (minus magnesium stearate)	Ratio 1.76:1

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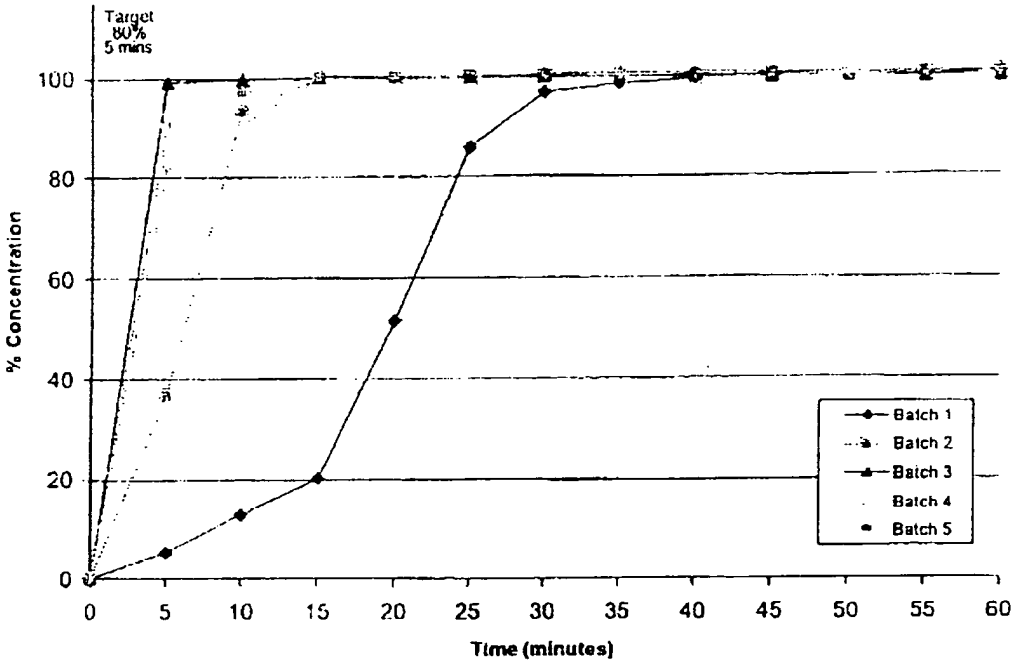
Study to investigate the effect of various ratios of MCC to SCG and other excipients and their effect on the disintegration of SCG tablets – basket method



	% Sample Concentration				
Time	Batch 1 —◆—	Batch 2 ···■···	Batch 3 —▲—	Batch 4 ·····	Batch 5 - - ✕ - -
0	0	0	0	0	0
5	5.2	36.8	99.1	81.4	90.4
10	13.1	93.4	99.7	90.5	97.1
15	20.1	99.8	100.1	99.8	100.4
20	51.2	99.8	100.1	99.7	100.1
25	86.0	100.2	100.1	99.8	100.3
30	97.1	99.9	100.2	99.9	100.4
35	98.5	99.9	100.0	100.0	100.5
40	99.4	99.9	100.2	99.5	100.6
45	99.8	100.1	99.8	100.0	100.6
50	99.8	100.6	100.0	99.9	100.5
55	100.3	99.8	99.9	100.1	100.6
60	100.6	100.4	100.0	100.0	100.7
Ratio (disintegrant to active)	Ratio 1.07:1	Ratio 1.36:1	Ratio 1.57:1	Ratio 1.76:1 (minus magnesium stearate)	Ratio 1.76:1

SCG Tablet Dissolution Profile

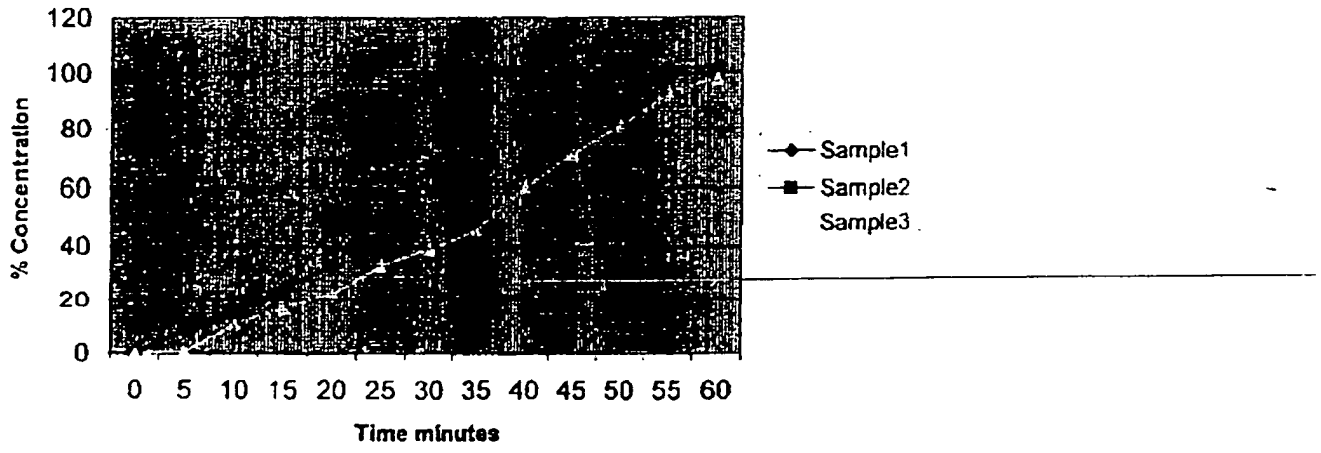
Core Tablets Batch #1

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
5	8.1	9.1	0.6
10	16.5	15.1	10.8
15	24.9	22.5	16.7
20	33.4	48.3	22.7
25	79.3	86.5	33.2
30	96.2	96.9	39.1
35	101.9	99.6	45.9
40	101.9	99.7	60.3
45	101.9	99.9	70.8
50	102.2	99.9	80.9
55	102.1	99.6	92.9
60	102.1	99.7	98.2

Formulation Ratio: 1:1 SCG Granule 115.85g ; Avicel 115.85g + Mag stearate 1.16g

Note: During dissolution it was noted that tablet 3 did not break up ie. kept it's shape until 30-40 minutes.

SCG Tablet Dissolution Profile Batch #1

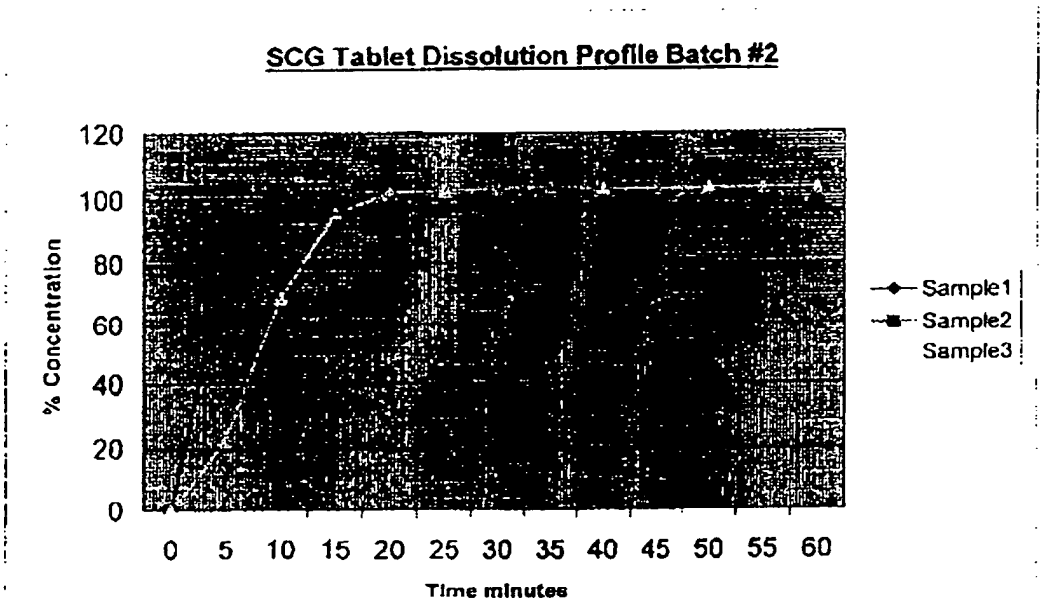


SCG Tablet Dissolution Profile

Core Tablets Batch #2

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
5	78.4	81	22.9
10	96.1	96.3	68.9
15	97.7	96.7	96.2
20	98	97.1	102
25	97.9	97	102.9
30	98	97.1	103.3
35	98	97.1	103.9
40	98.1	97.1	103.3
45	98	97.4	103.3
50	97.8	97.3	103.5
55	97.5	97.8	103.5
60	98.3	98.2	103.4

Formulation Ratio: 1:1.2 SCG Granule 115.85g : Avicel 139.02g + Mag stearate 1.27g



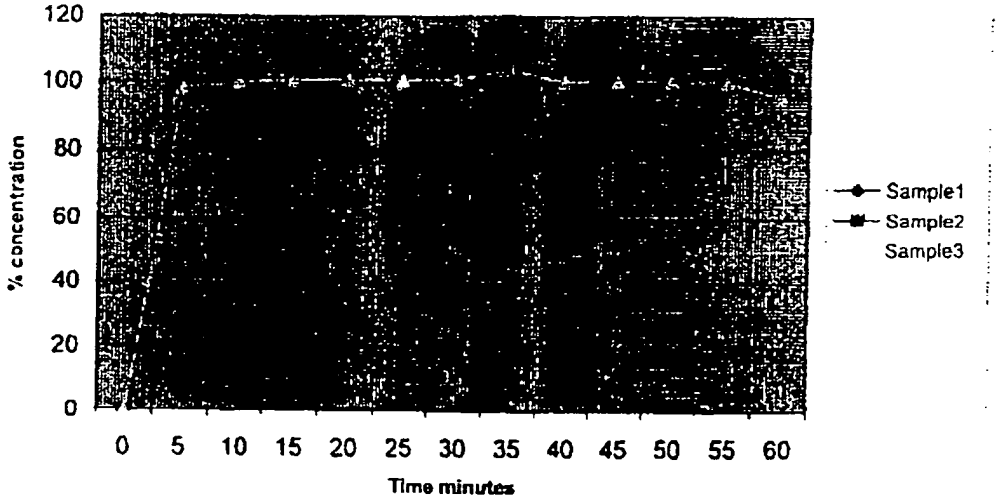
SCG Tablet Dissolution Profile

Core Tablets Batch #3

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
5	100.2	100.6	98.3
10	102.9	102.8	99.9
15	103.4	103.5	100.4
20	103.3	103.7	100.6
25	103.6	103.2	100.7
30	103.7	103.5	101
35	100.4	103.5	103.8
40	103.9	103.6	100.3
45	103.8	102.4	100.6
50	103.9	102.3	100.5
55	103.8	102.2	100.1
60	103.5	99.6	95.6

Formulation Ratio: 1.1:4 000 Granule 115.65g : Avicel 102.15g + Mag Stearate 1.4g

SCG Tablet Dissolution Profile Batch #3



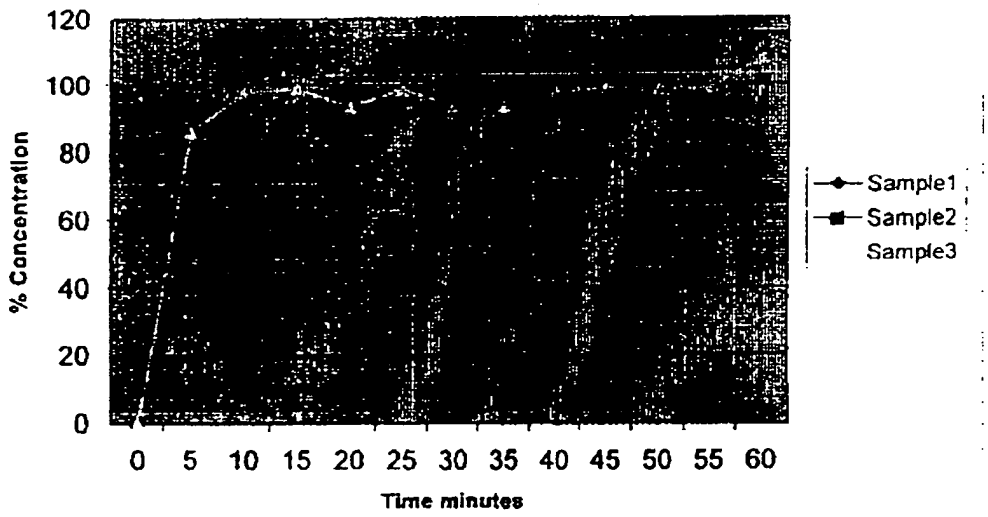
SCG Tablet Dissolution Profile

Core Tablets Batch #4

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
20	93.8	95.7	93.5
25	94.6	90.2	98.6
30	94.6	98.9	93.4
35	95.2	98.7	93.4
40	95.4	94.4	97.7
45	95	95.9	98.8
50	96.3	95.5	98.5
55	92.7	95.8	98.7
60	92.8	101.2	107.6

Formulation Ratio: 1:1.57 SCG Granule 115.85g : Avicel 182.65g + Mag stearate 0.0g

SCG Tablet Dissolution Profile Batch #4



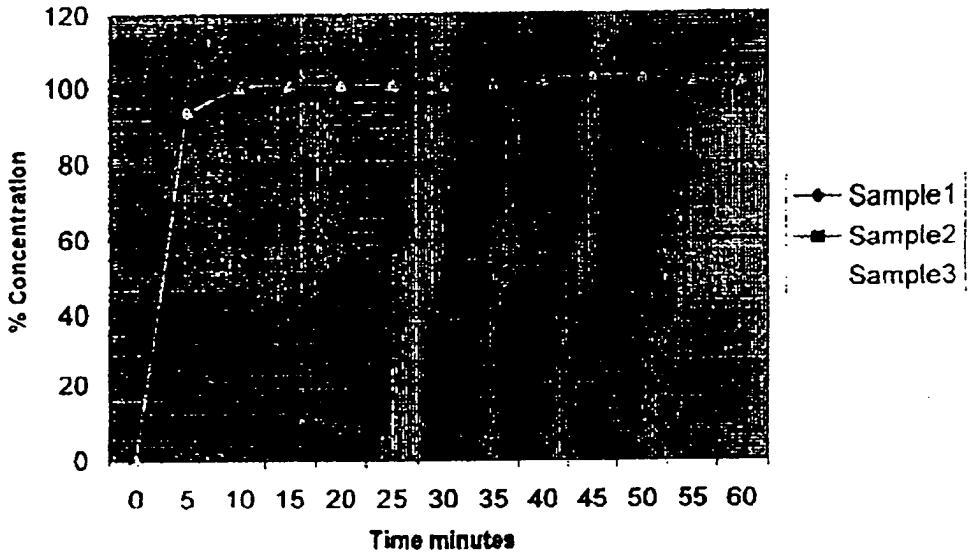
SCG Tablet Dissolution Profile

Core Tablets Batch #5

Time	% Sample Concentration		
	Sample1	Sample2	Sample3
0	0	0	0
5	92.1	91.4	93.7
10	99.7	99.3	100.1
15	100.9	100.8	100.7
20	101.1	100.5	100.6
25	101	102.4	100.5
30	100.6	100.6	100.4
35	100.8	100.5	100.7
40	102.1	103.1	101.7
45	100.6	103.6	103.1
50	100.7	103.1	102.6
55	100.6	103.7	101.4
60	98.9	101.4	101.3

Formulation Ratio: 1:1.57 SCG Granule 115.85g : Avicel 182.65g + Mag stearate 1.5g

SCG Tablet Dissolution Profile Batch #5



6. That based upon my experience, I am fully confident that the Watts et al. (U.S. 6,200,602) reference fails to teach or suggest the unexpected beneficial results of the pharmaceutical compositions embodied in the presently pending claims;

7. That this Declaration is given for the purpose of defining and delineating distinctions present in the claimed subject matter of this application from the disclosure available in the reference being relied upon by the Examiner, and that this Declaration is given in support of the patentability of the claims presently under consideration.

I declare under penalty of perjury under the Laws of the United States of America, that the foregoing is true and correct.

Executed on 22nd May, 2003 by:

Alexander James Wigmore.

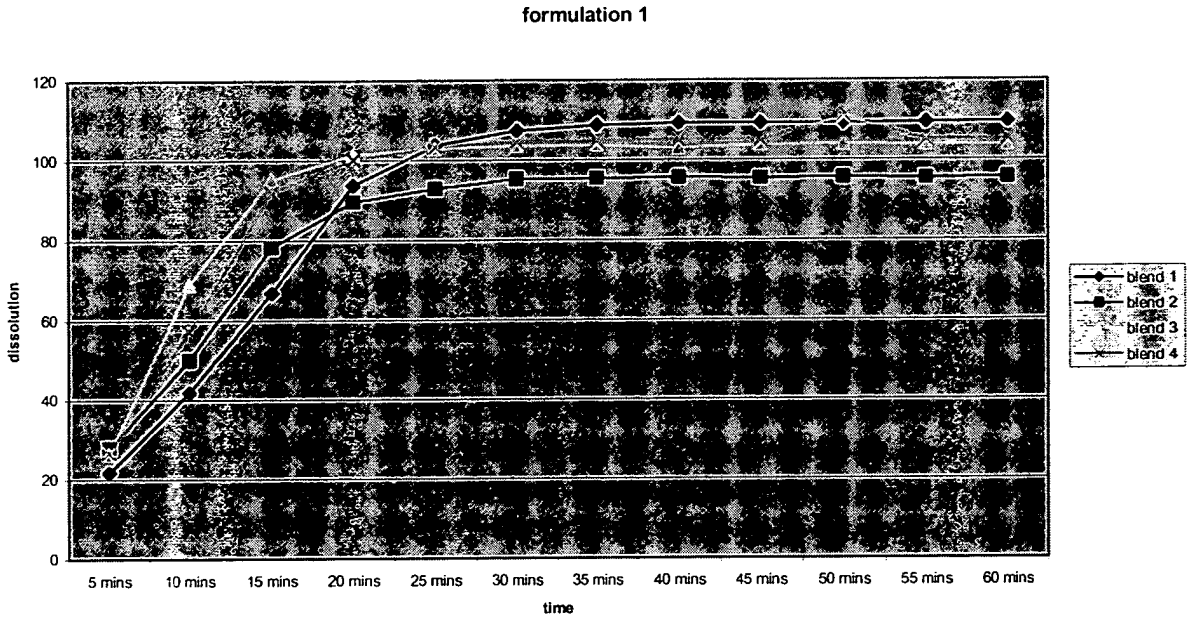
Alexander J. Wigmore.

EXHIBIT B

Experimental Results Submitted on April 30, 2004

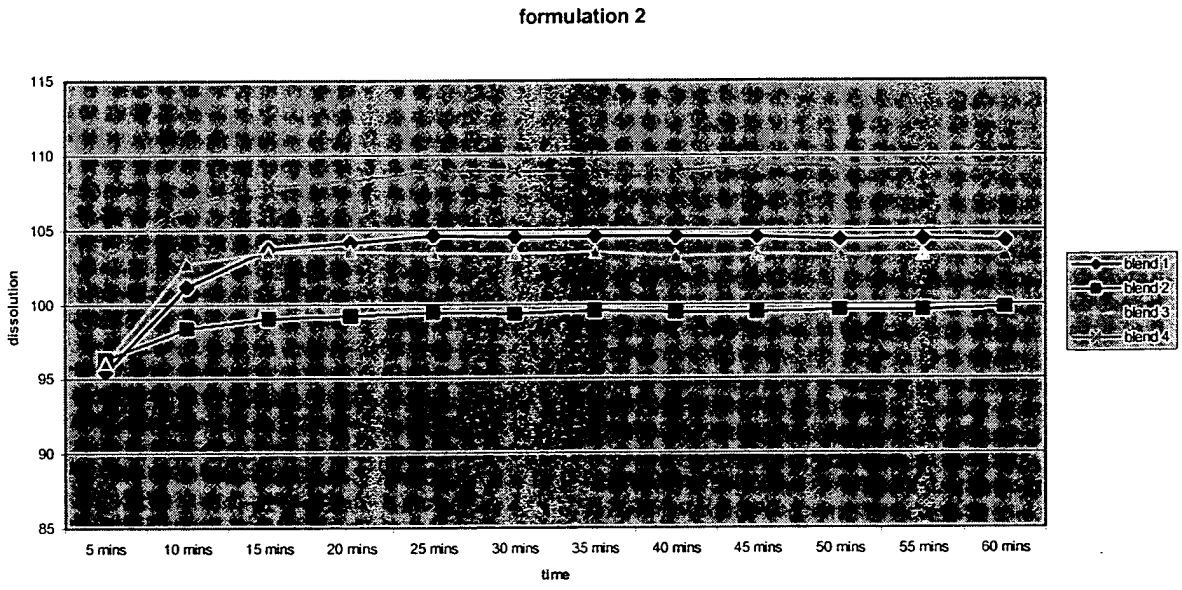
AVERAGE DISSOLUTION RESULTS FOR EACH FORMULATION

FORMULATION 1



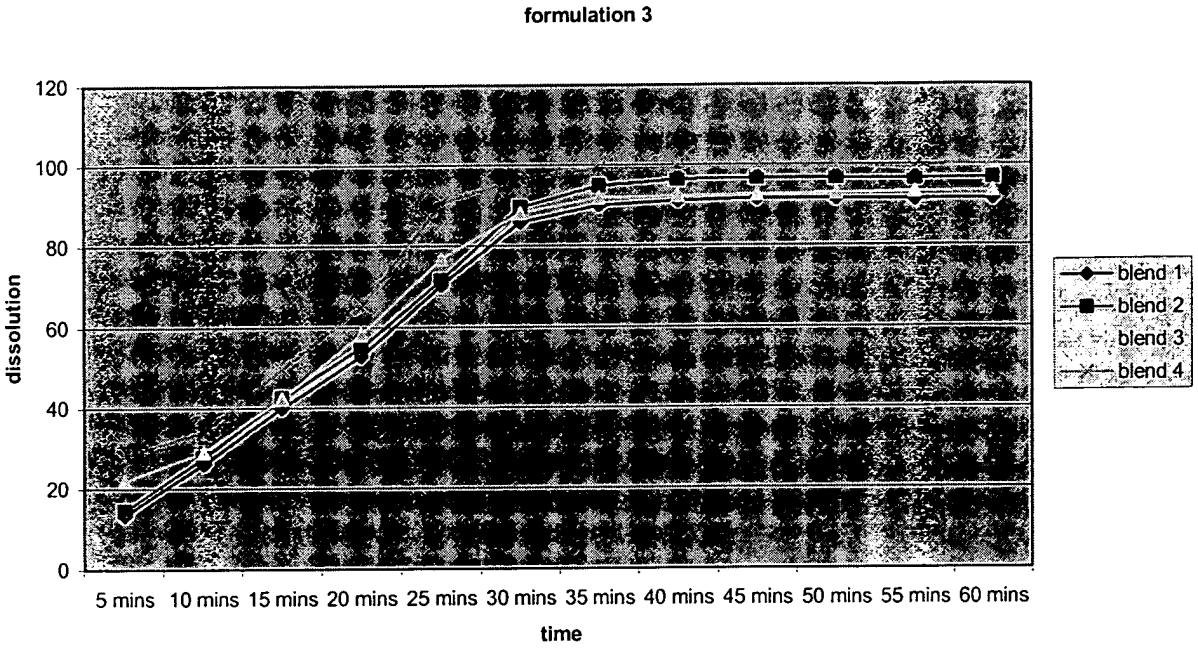
time	blend 1	blend 2	blend 3	blend 4
5 mins	21.71	27.93	26.43	26.72
10 mins	41.84	50.02	68.99	57.21
15 mins	66.87	78.3	95.21	91.98
20 mins	93.61	89.6	101.27	100.05
25 mins	103.64	92.87	102.87	103.21
30 mins	107.37	95.19	103.53	104.57
35 mins	108.63	95.3	103.61	104.74
40 mins	109.1	95.57	102.88	104.89
45 mins	109.2	95.39	103.67	104.98
50 mins	109.14	95.53	103.77	110.65
55 mins	109.29	95.44	103.62	104.87
60 mins	109.53	95.6	103.74	105.05

FORMULATION 2



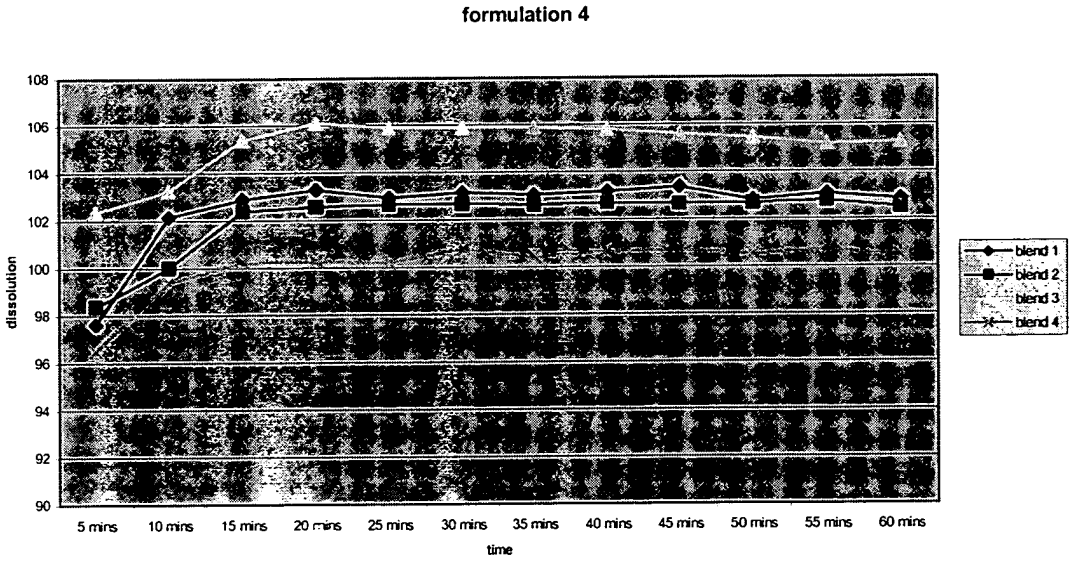
time	blend 1	blend 2	blend 3	blend 4
5 mins	95.43	96.3	96.1	103.21
10 mins	101.19	98.39	102.76	106.68
15 mins	103.72	99.04	103.53	107.92
20 mins	104.16	99.22	103.55	108.31
25 mins	104.62	99.42	103.45	108.99
30 mins	104.53	99.36	103.4	108.91
35 mins	104.57	99.55	103.53	108.93
40 mins	104.55	99.42	103.23	108.93
45 mins	104.54	99.45	103.35	109.31
50 mins	104.37	99.62	103.31	109.24
55 mins	104.41	99.6	103.34	109.31
60 mins	104.22	99.75	103.32	109.19

FORMULATION 3



time	blend 1	blend 2	blend 3	blend 4
5 mins	13.51	14.52	21.97	28.32
10 mins	26.29	27.75	29.19	34.22
15 mins	40.09	42.51	42.39	49.72
20 mins	52.77	54.93	58.17	64.93
25 mins	70.4	71.61	76.87	90.53
30 mins	85.89	89.61	88.1	96.72
35 mins	89.98	94.83	91.95	99.17
40 mins	91.19	96.44	92.36	99.56
45 mins	91.53	96.69	92.72	99.7
50 mins	91.53	96.75	92.92	99.59
55 mins	91.48	96.62	93.32	99.3
60 mins	91.56	96.68	93.41	101.235

FORMULATION 4



time	blend 1	blend 2	blend 3	blend 4
5 mins	97.63	98.38	102.35	96.53
10 mins	102.16	100.02	103.26	99.42
15 mins	102.89	102.39	105.38	100.23
20 mins	103.29	102.56	106.11	100.28
25 mins	102.95	102.64	105.89	100.2
30 mins	103.15	102.68	105.88	100.79
35 mins	103.04	102.62	105.89	100.42
40 mins	103.18	102.71	105.82	100.66
45 mins	103.36	102.64	105.61	100.73
50 mins	102.8	102.68	105.44	100.51
55 mins	103.08	102.79	105.18	100.72
60 mins	102.84	102.5	105.26	100.44

Sodium Cromoglycate Tablet Development & Dissolution Study

Background: A tablet formulation had previously been developed for the oral delivery of SCG. During the development of the tablet formulation, a study had been performed to identify the optimum SCG:MCC ratio for rapid tablet dissolution. Four tablet blends had been produced with varying SCG:MCC ratios and the dissolution profiles of each recorded.

Current Study Objective: To investigate the effects of replacing MCC with various other disintegrants.

Process: Four batches of granules were prepared, each containing a different disintegrant as follows:

Formulation 1	- Croscarmellose Sodium
Formulation 2	- Crospovidone
Formulation 3	- Sodium Starch Glycolate
Formulation 4	- Croscarmellose Na : MCC (1:9)

Each batch of granules was then divided into four sub-batches and blended with varying amounts of disintegrant (to match the SCG:MCC ratios of the original study). The sub-batches (blends) were then compressed into tablets using the rotary tablet press and dissolution tested in the laboratory so that their release profiles could be compared.

The SCG : Disintegrant ratios for each formulation were as follows:

Blend 1	1 : 1
Blend 2	1 : 1.2
Blend 3	1 : 1.4
Blend 4	1 : 1.6

Three tablets from each blend were dissolution tested in phosphate buffer. Samples of dissolution media were taken every 5 minutes over a 60 minute test period. The mean percentage dissolution was calculated for each blend at each timepoint and plotted for comparison (Appendix 1). The results were expressed as percentages of the theoretical SCG dose (calculated according to formulation and actual tablet weight).

Discussion:

Formulation 1 (Croscarmellose Sodium): The tablets from all four blends had reached their maximum dissolution at approximately 25 - 30 minutes. At 15 minutes, however, there was a marked difference between the performance of the Blends. Those with less disintegrant (1 & 2) had released significantly less SCG than those with more (3 & 4). The release

profiles of Blends 3 and 4, however, were very similar, suggesting the optimum SCG : Disintegrant ratio is approximately 1 : 1.4.

Formulation 2 (Crospovidone): The tablets from all four blends dissolved very rapidly. Each Blend achieved greater than 95% dissolution within 5 minutes. If the results were normalised so the maximum dissolution value achieved is taken as 100%, Blend 2 would be seen to dissolve quicker than the others initially, suggesting an optimum SCG : Disintegrant ratio of 1 : 1.2.

Formulation 3 (Sodium Starch Glycolate): The tablets from all four blends were slow to dissolve relative to the batches made with other disintegrants. This would suggest that sodium starch glycolate is least suitable for use as the disintegrant in the SCG tablet formulation.

Formulation 4 (Croscarmellose Sodium : MCC (1 : 9)): These tablet formulations (of the four included in this study) were the closest to the MCC-containing formulations in the original work. The variation was the addition of Croscarmellose Sodium at a ration of 1:9 to the MCC. The resulting tablets disintegrated very rapidly, but if the results were normalised to 100% Blend 3 would demonstrate the most rapid initial rate of dissolution. This result mirrored the observations made in the original and would suggest an optimum SCG : Disintegrant ratio of 1 : 1.4.

Appendices: Appendix 1 - Dissolution Data

SODIUM CROMOGLYCOLATE TABLET DEVELOPMENT AND DISSOLUTION STUDY

Four Tablet formulations used to produce 4 blends each - TOTAL = 16 Blends

DISSOLUTION PROFILES (60 minutes)

Formulation 1 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	19.62	23.24	22.26	21.71
10 mins	39.95	42.46	43.12	41.84
15 mins	61.61	67.98	71.03	66.87
20 mins	92.71	93.84	94.27	93.61
25 mins	103.29	102.49	105.13	103.64
30 mins	107.25	105.51	109.35	107.37
35 mins	108.12	106.8	110.97	108.63
40 mins	108.35	107.61	111.33	109.1
45 mins	108.39	107.46	111.76	109.2
50 mins	108.63	107.5	111.3	109.14
55 mins	108.53	107.61	111.74	109.29
60 mins	108.94	107.94	111.72	109.53

Formulation 1 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	29.51	27.2	27.08	27.93
10 mins	50.51	52.63	46.93	50.02
15 mins	80.07	78.84	75.99	78.3
20 mins	89.11	89.04	90.65	89.6
25 mins	92.13	91.91	94.58	92.87
30 mins	94.29	94.04	97.23	95.19
35 mins	94.29	94.15	97.45	95.3
40 mins	94.26	94.47	97.97	95.57
45 mins	94.35	94.19	97.64	95.39
50 mins	94.61	94.19	97.79	95.53
55 mins	94.3	94.32	97.71	95.44
60 mins	94.39	94.4	98.01	95.6

Formulation 1 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	26.75	24.64	27.91	26.43
10 mins	78.87	62.65	65.45	68.99
15 mins	89.24	97.38	99.01	95.21
20 mins	92.57	102.48	108.76	101.27
25 mins	93.08	104.48	111.05	102.87
30 mins	93.33	105.19	112.07	103.53
35 mins	93.44	105.14	112.26	103.61
40 mins	93.45	105.26	109.92	102.88
45 mins	93.35	105.4	112.25	103.67
50 mins	93.5	105.41	112.39	103.77
55 mins	93.52	104.98	112.37	103.62
60 mins	93.58	105.18	112.46	103.74

Formulation 1 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	26.661	25.799	27.689	26.72
10 mins	53.784	57.822	60.031	57.21
15 mins	93.567	96.829	83.963	91.98
20 mins	100.524	101.962	97.653	100.05
25 mins	102.461	103.522	103.641	103.21
30 mins	103.491	104.218	106	104.57
35 mins	103.569	104.202	106.459	104.74
40 mins	103.935	104.277	106.454	104.89
45 mins	103.837	104.595	106.506	104.98
50 mins	120.779	104.442	106.733	110.65
55 mins	103.763	104.35	106.492	104.87
60 mins	103.712	104.258	107.183	105.05

Formulation 2 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	93.973	94.385	97.944	95.43
10 mins	100.802	100.836	101.946	101.19
15 mins	103.025	104.278	103.851	103.72
20 mins	103.249	104.924	104.319	104.16
25 mins	104.065	105.38	104.399	104.62
30 mins	104.049	105.325	104.239	104.53
35 mins	103.964	105.321	104.474	104.57
40 mins	103.969	105.428	104.257	104.55
45 mins	104.033	105.562	104.026	104.54
50 mins	103.666	105.289	104.14	104.37
55 mins	103.818	105.065	104.352	104.41
60 mins	103.63	105.179	103.837	104.22

Formulation 2 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	94.923	98.831	95.146	96.3
10 mins	96.804	100.758	97.614	98.39
15 mins	97.91	100.911	98.309	99.04
20 mins	97.573	101.277	98.806	99.22
25 mins	97.424	101.267	99.198	99.42
30 mins	97.687	101.385	99.018	99.36
35 mins	97.985	101.564	99.097	99.55
40 mins	97.538	101.497	99.237	99.42
45 mins	97.623	101.72	99.017	99.45
50 mins	98.05	101.619	99.184	99.62
55 mins	97.687	101.722	99.38	99.6
60 mins	97.983	101.563	99.687	99.75

Formulation 2 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	97.55	98.711	92.029	96.1
10 mins	102.47	102.791	103.033	102.76
15 mins	103.007	103.497	104.092	103.53
20 mins	103.072	103.624	103.942	103.55
25 mins	102.74	103.499	104.114	103.45
30 mins	102.92	103.375	103.894	103.4
35 mins	103.043	103.53	104.03	103.53
40 mins	102.836	103.168	103.698	103.23
45 mins	102.749	103.491	103.815	103.35
50 mins	102.98	103.296	103.654	103.31
55 mins	102.886	103.296	103.826	103.34
60 mins	102.687	103.515	103.754	103.32

Formulation 2 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	101.137	101.893	106.589	103.21
10 mins	107.119	106.983	105.924	106.68
15 mins	108.972	108.622	106.177	107.92
20 mins	109.708	109.057	106.159	108.31
25 mins	110.448	109.678	106.877	108.99
30 mins	110.33	109.546	106.844	108.91
35 mins	110.243	109.498	107.054	108.93
40 mins	110.322	109.67	106.796	108.93
45 mins	110.595	109.929	107.395	109.31
50 mins	110.416	110.178	107.135	109.24
55 mins	110.95	109.912	107.066	109.31
60 mins	110.514	109.909	107.142	109.19

Formulation 3 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	14.723	13.005	12.809	13.51
10 mins	27.436	25.241	26.19	26.29
15 mins	40.544	39.241	40.482	40.09
20 mins	52.543	52.003	53.778	52.77
25 mins	74.935	64.043	72.217	70.4
30 mins	82.997	87.892	86.77	85.89
35 mins	85.283	93.045	91.626	89.98
40 mins	85.75	94.659	93.164	91.19
45 mins	85.969	95.04	93.59	91.53
50 mins	86.098	94.991	93.499	91.53
55 mins	85.785	95.037	93.611	91.48
60 mins	86.117	95.076	93.477	91.56

Formulation 3 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	15.727	14.685	13.153	14.52
10 mins	29.844	28.56	24.846	27.75
15 mins	45.383	45.079	37.074	42.51
20 mins	58.437	58.348	48.012	54.93
25 mins	84.183	72.391	58.249	71.61
30 mins	92.421	93.551	82.866	89.61
35 mins	94.067	99.277	91.16	94.83
40 mins	94.992	100.669	93.661	96.44
45 mins	94.611	101.152	94.292	96.69
50 mins	94.735	100.772	94.728	96.75
55 mins	94.61	100.912	94.335	96.62
60 mins	94.54	100.782	94.708	96.68

Formulation 3 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	21.389	21.069	23.464	21.97
10 mins	29.02	27.295	31.246	29.19
15 mins	42.048	40.732	44.392	42.39
20 mins	60.713	54.234	59.564	77.33
25 mins	71.087	78.519	81.008	76.87
30 mins	91.611	84.935	87.754	88.1
35 mins	98.693	87.188	89.976	91.95
40 mins	98.451	88.013	90.601	92.36
45 mins	98.811	88.376	90.96	92.72
50 mins	99.282	88.504	90.982	92.92
55 mins	99.639	88.942	91.381	93.32
60 mins	99.451	89.025	91.742	93.41

Formulation 3 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	29.087	29.668	26.195	28.32
10 mins	33.751	34.982	33.931	34.22
15 mins	48.482	50.128	50.539	49.72
20 mins	63.326	65.963	65.49	64.93
25 mins	90.564	91.015	89.996	90.53
30 mins	96.456	96.211	97.497	96.72
35 mins	98.919	99.034	99.569	99.17
40 mins	98.818	99.946	99.927	99.56
45 mins	99.273	99.878	99.939	99.7
50 mins	98.76	99.992	100.019	99.59
55 mins	99.606	98.762	99.529	99.3
60 mins	99.051	100.16	101.235	100.15

Formulation 4 Blend 1

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	99.832	97.413	95.652	97.63
10 mins	102.841	103.899	99.738	102.16
15 mins	103.244	104.676	100.761	102.89
20 mins	103.674	105.057	101.147	103.29
25 mins	103.35	104.975	100.523	102.95
30 mins	103.535	105.011	100.895	103.15
35 mins	103.385	104.92	100.821	103.04
40 mins	103.62	104.942	100.979	103.18
45 mins	103.035	104.925	100.564	103.36
50 mins	103.24	104.785	100.375	102.8
55 mins	103.407	105.157	100.681	103.08
60 mins	103.331	104.819	100.383	102.84

Formulation 4 Blend 2

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	99.112	93.724	102.317	98.38
10 mins	101.597	92.171	106.278	100.02
15 mins	102.476	98.323	106.381	102.39
20 mins	102.55	98.538	106.582	102.56
25 mins	102.635	98.369	106.921	102.64
30 mins	102.642	98.487	106.903	102.68
35 mins	102.611	98.355	106.906	102.62
40 mins	102.77	98.347	107.279	102.71
45 mins	102.509	98.414	106.582	102.64
50 mins	102.841	98.341	106.845	102.68
55 mins	102.956	98.395	107.018	102.79
60 mins	102.415	98.437	106.642	102.5

Formulation 4 Blend 3

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	99.844	105.363	101.856	102.35
10 mins	103.867	108.279	103.261	103.26
15 mins	104.721	108.467	102.95	105.38
20 mins	104.963	108.684	104.696	106.11
25 mins	104.86	108.648	104.15	105.89
30 mins	104.586	108.814	104.233	105.88
35 mins	104.629	109.042	104.004	105.89
40 mins	105.021	108.541	103.906	105.82
45 mins	104.581	108.573	103.679	105.61
50 mins	104.449	108.246	103.614	105.44
55 mins	104.132	107.929	103.478	105.18
60 mins	103.923	108.193	103.667	105.26

Formulation 4 Blend 4

		percentage dissolution		
time	tablet 1	tablet 2	tablet 3	mean
5 mins	98.457	93.7	97.422	96.53
10 mins	101.358	96.505	100.407	99.42
15 mins	101.783	97.487	101.424	100.23
20 mins	101.85	97.504	101.642	100.28
25 mins	102.01	97.13	101.457	100.2
30 mins	102.565	97.764	102.03	100.79
35 mins	102.029	97.595	101.634	100.42
40 mins	102.267	97.687	102.03	100.66
45 mins	102.47	97.801	101.927	100.73
50 mins	102.067	97.686	101.771	100.51
55 mins	102.429	97.524	102.192	100.72
60 mins	102.395	97.368	101.569	100.44

EXHIBIT C

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(54) Sodium cromoglycate reconstitutable powders

(57) A mixture useful in the treatment of conditions of the gastrointestinal tract of sodium cromoglycate of mass median diameter from 2 to 30 microns with a pharmaceutically acceptable water soluble carrier of sieve size from 200 to 1000 microns, the carrier having a solubility of greater than 1 to 5 by weight in water at 20°C and preferably comprising a sugar e.g. sucrose. The mixture may be formulated in sachets for dissolution in water prior to oral administration.

GB 2 086 227 A

SPECIFICATION

Pharmaceutical formulation

This invention relates to a new pharmaceutical formulation.

Sodium cromoglycate is well known to be useful, when administered by inhalation, for the treatment of asthma. For this use a dry powder mixture is sold comprising fine particles of the drug and coarser (30—80 micron) particles of lactose in a 1:1 weight ratio. This formulation has a slightly bitter taste. The objective in this formulation is to provide a composition in which the particles of drug adhere to the coarse lactose, but are capable of being shaken off the lactose in the airstream which is inhaled by the patient. This formulation is more fully described in British Patent Specification No. 1, 242, 211. A modification of this powder formulation in which the particle size of the lactose carrier is from 80 to 150 microns in size is disclosed in British Patent Specification No. 1, 381, 872 and a further modification in which the particle size of the drug is from 2 to 4 microns is disclosed in British Patent Specification No. 1, 410, 588.

Sodium cromoglycate has also been known for many years, e.g. from British Patent Specification No. 1, 423, 985, to be useful for the treatment of conditions of the gastro-intestinal tract. Various formulations have been suggested for this use including hard, dense granules of the drug (as described in British Patent Specification No. 1, 549, 229), which have been put up in a capsule which is designed to be swallowed. These granules can also be removed from the capsule and dissolved in water. However it has been found that the granules are slow to dissolve, and it has been found necessary to follow the tedious procedure of dissolving them in hot water to ensure complete dissolution, and then to dilute the resulting solution with cold water. Adding sodium cromoglycate powder directly to cold water results in dry, unwetted powder being trapped in a gel of dissolving sodium cromoglycate, and, in consequence, solution time is prolonged because of inadequate wetting/de-aeration. Food allergy is thought to start in the mouth, and the physicochemical properties of sodium cromoglycate, in relation to the anatomy and biochemical conditions of the gastro-intestinal tract, therefore indicate that it should be taken by the patient as a solution for maximum therapeutic benefit. These liquid formulations are *prima facie* attractive. However multidose liquid formulations inevitably require the inclusion of preservative substances which are undesirable in the treatment of the allergic conditions. Many of the conventionally used preservatives are chemically incompatible with sodium cromoglycate and the limited range of compatible substances have allergenic potential for the group of patients to be treated. On the other hand unit dose liquid forms of drugs are expensive, and are technically very difficult to produce, especially when formulated aseptically without a preservative. Indeed we are unaware of any unpreserved liquid unit dose drug formulation being available commercially. Furthermore liquid dosage forms of all kinds are expensive to transport and store because of their high volume and weight per unit dose.

Tablets containing the drug have been contemplated, but tablet formulations contain excipients, which, as with the preservatives conventionally used in solutions, tend to be allergenic. Furthermore tablets tend to take a long time to dissolve and are therefore inconvenient to the patient.

As a finely divided powder, which is a primary requisite for rapid dissolution, sodium cromoglycate is cohesive, and in pure form aggregates into a gel-like mass in contact with water, especially in cold drinking water.

We have now found, however, that certain therapeutically acceptable carrier materials, classified into particular sized particles, have the property of forming a uniform surface coating of sodium cromoglycate, even in the absence of binding agents. The resulting mixture is free flowing with a uniform distribution of the drug and has the particular advantage that it dissolves rapidly and completely in cold water. Furthermore the formulation can be readily filled into unit dose containers, e.g. sachets, whereby it can be protected from the damaging effects of atmospheric moisture.

This product form has the advantage that it is cheap to produce and distribute, it maximises the drug's bio-availability with the minimum of inconvenience to the patient, and by using a non-allergenic excipient it minimises the chance of any allergic response to the formulation itself. A particular advantage of the formulation is that by selecting a sweet-tasting carrier substance, the unpleasant taste of sodium cromoglycate can be masked acceptably without the need for an artificial flavouring agent. This is of particular value in the treatment of food allergic disease in children where the exclusion of artificial flavours in the diet is a pre-requisite of treatment and where, as with all patients, good compliance with the prescribed drug therapy is as difficult to achieve as it is essential.

As can be appreciated from the considerations set out above the pharmaceutical criteria which are applicable to oral and inhalation forms of the drug are entirely different, and indeed the medical conditions treated by the two different forms of the drug are dealt with by quite separate groups of medical specialist.

Thus, according to the invention we provide a mixture of sodium cromoglycate of mass median diameter from 2 to 30 microns with a pharmaceutically acceptable water soluble carrier of sieve size from 200 to 1000 microns, the carrier having a solubility of greater than 1 to 5 by weight in water at 20°C.

The finely divided sodium cromoglycate preferably has a mass median diameter of from 2 to

10 microns, and more preferably from 3 to 6 microns with 90% of the particles being of less than 30 microns diameter. The particle size of the sodium cromoglycate when below 10 microns may be measured by means of a Coulter counter. When above 10 microns the particle size may be measured by sieving.

The water soluble carrier preferably has a particle size of from 200 to 500 microns, e.g. a mean size of from 270 to 370 microns. The particle size of the water soluble carrier may be measured by sieving.

The water soluble carrier is preferably a sugar, for example xylitol and even more preferably sucrose, e.g. beet sucrose. We naturally prefer to avoid sugars which are poorly absorbed and which can, in certain circumstances, cause diarrhoea. We also prefer the sugar to be in a form which will dissolve quickly in water.

The water soluble carrier preferably has a solubility of greater than 1 to 4 more preferably greater than 1 to 2 and most preferably greater than 1 to 1.5, by weight in water at 20°C.

Sucrose is a particularly acceptable excipient for the formulation since it combines in one substance the merits of ready availability in appropriate size grades, cheapness, the desired physical characteristics for coating with the drug, good crystal strength with a rapid aqueous dissolution rate, freedom from allergenic potential, and a degree of sweetness appropriate to mask the taste of sodium cromoglycate in proportions which are pharmaceutically and medically acceptable. In addition it has a low moisture content and with the crystal size selected does not aggregate either in manufacture or storage.

When the formulation is added to cold water the coated carrier, e.g. sucrose particles, remain separate during the dissolution process and this ensures that the individual particles of sodium cromoglycate are uniformly wetted, thus promoting rapid drug dissolution without gelling.

Other sugars may be used in place of sucrose, but many have disadvantages. Thus glucose has a negative heat of solution which militates against ease of dissolution, lactose is insufficiently water soluble nor is it very sweet and, because of its origins, may contain allergic impurities, and xylitol is expensive and is not readily available in the desired particle size.

We prefer the composition to contain an excess, e.g. a 2 to 20 times, and preferably a 4 to 15 times by weight excess, of the water soluble carrier, e.g. sugar, and especially just sufficient sugar to mask the taste of the sodium cromoglycate. The proportion of sugar will thus depend on the particular sugar used. However, we have found that with sucrose a suitable proportion is from 5 to 12, and especially from 7.5 to 10 parts by weight for each part by weight of sodium cromoglycate.

The formulation may be put up into unit dosages, e.g. sachets (which are preferably made of material which will prevent the ingress of water) containing from 50 to 300mg, e.g. 100 or 200mg, of sodium cromoglycate and from 1—3g, e.g. about 2g, of sugar. The unit doses may be administered from 1 to 6 times a day, preferably before, e.g. about 30 minutes before meals. The composition preferably contains a low proportion of 'heavy metal ions', as we have found that the presence of such ions tends to produce cloudy solutions when the composition is dissolved in water. By the term 'heavy metal ions' we mean ions of metals in groups IIa, Ib, IIb, IIIa, IVa and IVb of the periodic table and of the transition metals. Specific 'metal ions' which are detrimental, in excessive concentrations (i.e. above about 20 ppm) in solutions made up from the compositions of the invention, are Pb^{++}, Ca^{++}, Mg^{++} and in particular Fe^{++}, Fe^{+++} and Zn^{++} ions. We particularly prefer to keep the concentration of Mg^{++} ions as low as possible, e.g. less than about 0.22 ppm.

The composition also preferably contains a low proportion of water, e.g. less than 2%, preferably less than 1% and typically about 0.5% by weight. We prefer to carry out the mixing, and forming of the mixture into unit doses, at a relative humidity of less than about 65%, e.g. from about 40 to 65%.

The composition preferably comprises particles of the relatively coarse carrier coated with a layer of the fine sodium cromoglycate. We have surprisingly found that we can achieve the same effect as with the so called 'ordered mixing' with many times larger proportion of fine sodium cromoglycate to carrier than would be expected from theoretical considerations. The composition also desirably is such that there is no caking of the blend between mixing and formation into unit dosages, e.g. sacheting. The mixture also desirably is such that there is no, or very little, segregation when it is filled, stored and transported.

We prefer the composition to contain no other excipients than the water soluble carrier.

The compositions of the invention can be used in the treatment of a wide variety of conditions, e.g. Crohn's disease (a condition of the small, and sometimes also of the large, intestine), atrophic gastritis (a condition of the stomach), ulcerative colitis (a condition of the rectum), proctitis (a condition of the rectum and lower large intestine), coeliac disease (a condition of the small intestine), regional ileitis (a regional inflammatory condition of the terminal ileum), peptic ulceration (a condition of the stomach and duodenum), gastrointestinal allergy (e.g. milk, gluten, food additive etc. allergy), irritable bowel syndrome and gastrointestinal bleeding induced by administration of an anti-inflammatory, e.g. indomethacin or aspirin.

The composition is particularly useful for the treatment of food allergy in children.

The compositions of the invention may be made by mixing the fine sodium cromoglycate with the coarse carrier e.g. in a planetary or a matrix mixer. Desirably a three (or greater) layer sandwich of the

components is placed in the mixer before the mixing commences. The mixing should be carried out for a sufficient time to ensure as uniform a mix as possible. Mixing times of up to 60 minutes, but preferably of less than 15 minutes are generally suitable. The mixer is preferably such as not to change the particle sizes of the ingredients significantly during the mixing process.

The invention is illustrated but in no way limited by the following Examples.

EXAMPLE 1

Sodium cromoglycate (Apex milled mass median diameter 3—6 microns, greater than 90% less then 30 microns. Measured as 'anhydrous' material)	100mg	200mg	
Sucrose (Caster sugar sieve cut 90% greater than 150 microns, 90% less than 450 microns)	to 1.03g	2.01g	

A sandwich of sucrose-sodium cromoglycate-sucrose was placed in a matrix mixer (100L Fielder) in which a main rotor passed through the base of the powder and a side chopper rotor disrupts the mass movement of the powder. A satisfactory degree of mixing is achieved after a time of from about 2 to 10 minutes of operation of the mixer. The formulations are put up in paper/foil/polyethylene or 'Surlyn' laminate sachets; the individual sachets being 40 x 75mm and produced in strips of five 160 x 75mm with perforations between each. These strips are cartoned for appropriate treatment periods, e.g. 50's, 60's, 100's etc.

EXAMPLE 2

2g of the mixture of Example 1 when poured into 80ml of tap water at 25°C ± 3°C in a 100ml beaker stirred by a high speed stirrer (1200 rpm) dissolved (visual assessment) in 20—25 seconds. By way of contrast 200mg of granules of sodium cromoglycate mean size 120 microns took 45—50 seconds to dissolve.

CLAIMS

1. A mixture of sodium cromoglycate of mass median diameter from 2 to 30 microns with a pharmaceutically acceptable water soluble carrier of sieve size from 200 to 1000 microns, the carrier having a solubility of greater than 1 to 5 by weight in water at 20°C.

2. A mixture according to Claim 1, wherein the sodium cromoglycate has a mass median diameter of from 2 to 10 microns.

3. A mixture according to Claim 1 or 2, wherein the water soluble carrier has a particle size of from 200 to 500 microns.

4. A mixture according to any one of the preceding claims, wherein the water soluble carrier has a mean size of from 270 to 370 microns.

5. A mixture according to any one of the preceding claims, wherein the water soluble carrier is a sugar.

6. A mixture according to Claim 5, wherein the sugar is sucrose.

7. A mixture according to any one of the preceding claims, wherein the water soluble carrier has a solubility of greater than 1 to 4 by weight in water at 20°C.

8. A mixture according to Claim 7, wherein the water soluble carrier has a solubility of greater than 1 to 2 by weight in water at 20°C.

9. A mixture according to Claim 8, wherein the water soluble carrier, has a solubility of greater than 1 to 1.5 by weight in water at 20°C.

10. A mixture according to any one of the preceding claims containing an excess by weight of the water soluble carrier.

11. A mixture according to Claim 10 containing from 2 to 20 times by weight excess of the water soluble carrier.

12. A mixture according to Claim 11 containing from 4 to 15 times by weight excess of the water soluble carrier.

13. A mixture according to Claim 12 containing from 5 to 12 parts by weight of sucrose for each part by weight of sodium cromoglycate.

14. A mixture according to Claim 13 containing from 7.5 to 10 parts by weight of sucrose for each part by weight of sodium cromoglycate.

15. A mixture according to any one of the preceding claims in unit dosage form containing from 50 to 300mg of sodium cromoglycate.

16. A mixture according to Claim 15 containing 100 or 200mg of sodium cromoglycate.

17. A mixture according to Claim 15 or 16 in the form of a sachet.

18. A mixture according to Claim 17, wherein the sachet is made of material which will prevent

the ingress of water.

19. A mixture according to any one of the preceding claims containing a low proportion of 'heavy metal ions', as hereinbefore defined.

20. A mixture according to any one of the preceding claims containing less than 2% by weight of water.

21. A mixture according to Claim 20 containing less than 1% by weight of water.

22. A mixture according to any one of the preceding claims containing no other excipient than the water soluble carrier.

23. A method of making a mixture according to Claim 1 which comprising mixing the components at a relative humidity of less than 65%.

24. A method according to Claim 23, wherein the relative humidity is from 40 to 65%.

25. A mixture according to Claim 1 and substantially as hereinbefore described in Example 1.

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10. Appendix of Related Proceedings (37 CFR §41.37(c)(1)(x):

None.

CERTIFICATE OF MAILING

I hereby certify that the foregoing Appeal Brief in application Serial No. 09/531,681, filed May 10, 2001 of Alexander James Wigmore, entitled "TREATMENT OF ALLERGIC CONDITIONS" along with a transmittal cover letter an Exhibits A-C are being deposited with the United States Postal Service as First Class mail, postage prepaid, in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 20th day of January, 2006.

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Date of Signature: Jan. 20, 2006